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EXAMINER	
BERCH, MARK L	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,853	WILSON ET AL.	
	Examiner	Art Unit	
	/Mark L. Berch/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/08/2005;02/06/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over 6489332 or 5786360 or WO 2003103675A2.

The narrow claims of the 6489332 reference teach, with one exception, the subject matter of claims 1-33. Note that R7 can be H or amino or in claim 13 is hydroxyethyl or carboxyvinyl; R5 is ethyl and R6 is H or hydroxyethyl, and n=2. Probes are taught in the paragraph bridging columns 4-5 and the following two paragraphs. Pharmaceutical uses appear at column 6, lines 18-20. The sole difference is that in Neely, the R8 substituent (which can be amino or hydroxyethyl as seen in the claims) is present at the para position, whereas in the claims, it is at the ortho or meta position (see third from last line of page 30). It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: ***Ex parte Englehardt***, 208 USPQ 343, 349; ***In re Mehta***, 146 USPQ 284, 287; ***In re Surrey***, 138 USPQ 67; ***Ex Parte Ullyot***, 103 USPQ 185; ***In re Norris***, 84 USPQ 459; ***Ex***

Parte Naito, 168 USPQ 437, 439; ***Ex parte Allais***, 152 USPQ 66; ***In re Wilder***, 166 USPQ 545, 548; ***Ex parte Henkel***, 130 USPQ 474; ***Ex parte Biel***, 124 USPQ 109; ***In re Petrzilka***, 165 USPQ 327; ***In re Crownse***, 150 USPQ 554; ***In re Fouche***, 169 USPQ 431; ***Ex parte Ruddy***, 121 USPQ 427; ***In re Wiechert***, 152 USPQ 247, ***In re Shetty***, 195 USPQ 753; ***In re Jones***, 74 USPQ 152, 154; and ***In re Mayne***, 41 USPQ2d 1451 (in which the Court took notice of the extreme similarity between the amino acids Leucine and isoleucine: "In fact, Leu is an isomer of Ile -- an identical chemical formula with differences only in the chemical bonding of the atoms. The side chains...of Leu and Ile have the same number of hydrogen and carbon atoms...The structure of Leu and Ile alone suggest their functional equivalency" (at 1454-1455)).

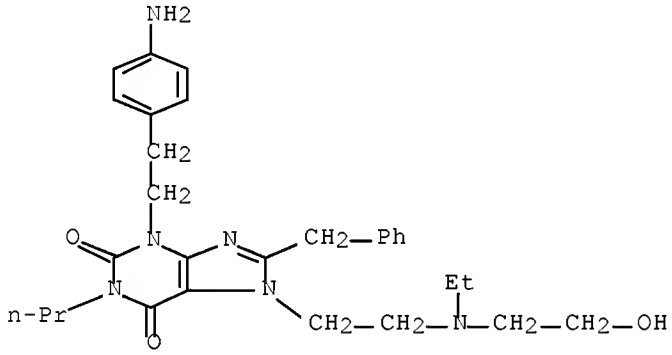
For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (Englehardt) and "Position isomerism is a fact of close structural similarity" (Mehta, emphasis in the original). Note also ***In re Jones***, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to prima facie obviousness"; one of those listed is "adjacent homologues and structural isomers". Position isomers are the basic form of close "structural isomers." Similar is ***In re Schechter and LaForge***, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also ***In re Deuel*** 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds ... a known compound may suggest its

analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para)." See also MPEP 2144.09, second paragraph.

With regard to the synthesis, although the claims recite the use of the acid R3COOH to do the cyclization, and the reference has the aldehyde, the aldehyde in the reference is reacted with an oxidant (e.g. NaIO4; see column 7) which will convert the aldehyde into the acid so that the same step is actually involved.

In 5786360, see same species at claims 4, 7, 10 and 13 (two species).

The reference WO 2003103675A2 shows compound II on pages 13-14, which is this:



This again is a position isomer.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-28, 30, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The nature of the "spacer" is unknown. It states where something is, but not what it is. It mentions having a "functionality which bonds..." but almost anything will bond to a N or O atom.
2. The scope of the "label" is also unclear. Without knowing what it is supposed to diagnose, it is unknown what sorts of things will qualify as labels and what will not.
3. AIDS is listed twice in claim 28.
4. The term "Diabetes" is ambiguous. It is not a complete term. Diabetes insipidus for example is caused by the inability of the kidneys to conserve water, which is caused by a lack of ADH (central diabetes insipidus) or by failure of the kidneys to respond to ADH (nephrogenic diabetes insipidus). Applicants must select some specific form(s) of diabetes (e.g. Type 2 diabetes mellitus, maturity-onset diabetes of the young (MODY, which comes in 6 completely different forms arising from different genetic defects), Gestational diabetes mellitus ("GD") and neonatal diabetes, which also arises from a specific genetic defect; these are metabolic disorders) and they must use that term, and show that one of ordinary skill in the art would have been able to determine that whatever term(s) is/are selected was the one(s) intended.
5. Claim 30 is unclear. It says "A prodrug comprising a compound according to claim 1". As written, it is identical to claim 1, simply calling the material of Formula I a prodrug. Hence, it is improperly dependent on claim 1 as it does not further limit the claim. Alternatively, applicants may intended a prodrug of the claimed of claim 1. If so, then a)

the wording must be changed to actually say that and b) the claim would again be improperly dependent on claim 1 as claim 1 makes no provision in the first place for a prodrug.

6. In claim 17, what are these "atoms bonded thereto"? What kind of atoms, and bonded where and how? How many atoms can there be in this bonding?
7. Claim 32 has "strong base". Where is the line between acids which are storng and those which are not?

Claims 22-27, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"A1 adenosine receptor related disorders" recited in claim 22 and 31 is of unknown scope. The scope of adenosine A1 related disorders is unclear. The A1 receptor is involved with bradycardia, inhibition of lipolysis, reduced glomerular filtration, tubero-glomerular feedback, antinociception, reduction of sympathetic and parasympathetic inhibition, neuronal hyperpolarization, ischemic preconditioning and many other things. It would also cover diseases which damage the A1 receptor and which will cause the body to grow more such receptors. It would cover disease which are caused by both overactivity and under-activity of the receptor.

Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for solvates/hydrates. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace solvates or hydrates are not enabled. The numerous examples presented all failed to produce a solvate. The evidence of the specification is thus clear: These compounds do not possess the property of forming solvates; there is no evidence that such compounds even exist. Thus, this is a circumstance where the "specification is evidence of its own inadequacy" (***In re Rainer***, 377 F.2d 1006, 1012, 153 USPQ 802, 807). These cannot be simply willed into existence. As was stated in ***Morton International Inc. v. Cardinal Chemical Co.***, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Claims 22-28 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to ***In re Wands***, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the

prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see ***In re Vaeck***, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to large number of primary variables, millions of compounds are embraced.

(b) Scope of the diseases covered. As is noted above, the scope of disorders is unknown. In this analysis which follows, the claim 28 language is used.

I. The scope of treating inflammation generally is extraordinarily broad. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. It is one of the most pervasive of all body processes. Inflammation is a very general term which encompasses a huge variety of specific processes.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The

hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Mechanistically, chronic inflammation encompasses a broad spectrum of immunologic processes, including antibody formation, antibody-dependent cell-mediated cytotoxicity, and cell-mediated immunity (delayed-type hypersensitivity). Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae.

Cystitis is any inflammation of the bladder, often caused by bacteria. Two ordinary types are eosinophilic and tuberculous cystitis. Interstitial cystitis (IC) is a particularly severe form, an inflammation of the bladder wall which may include Glomerulations. The origins and mechanism are largely unknown, and it isn't even clear whether there is just one form of the disease or several. There is no actual pharmaceutical treatment for the disease itself, although a few drugs can give some relief of symptoms, specifically Elmiron and DMSO.

Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

There is also a wide assortment of forms of conjunctivitis, including seasonal allergic conjunctivitis, perennial allergic conjunctivitis, giant papillary conjunctivitis (GPC) (a chronic yet poorly condition associated with contact lens wear), Vernal keratoconjunctivitis and atopic keratoconjunctivitis. In addition to types of allergic conjunctivitis there is also bacterial conjunctivitis (e.g. from Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus) and viral conjunctivitis (e.g. from gonorrhea, herpes simplex, chlamydia, adenoviruses or enteroviruses) Parasitic conjunctivitis (e.g. from ***Onchocerca volvulus***, ***Loa loa***, ***Wuchereria bancrofti*** or ***Trichinella spiralis)***, fungal conjunctivitis (e.g. from ***Candida albicans*** or ***Sporothrix schenckii)***, Phlyctenular Conjunctivitis, Inclusion Conjunctivitis, immunologic conjunctivitis, irritant conjunctivitis (e.g. from burns, chlorine or air pollutants), Radiation conjunctivitis, and assorted forms of neonatal conjunctivitis (which can be caused by e.g. a blocked tear duct).

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as Salmonella, Staphylococcus, Streptococcus (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

The term "arthritis" is used for any of the dozens of kinds of inflammation of the joints arising from a wide diversity of causes and mediators, many of which are unknown. It mostly commonly refers to any of osteoarthritis, gouty arthritis, or rheumatoid arthritis. These are three totally different and unrelated disorders, which all have "arthritis" in their

name and involve inflammation of the joints. Rheumatoid arthritis is an inflammatory disorder causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, TNF-I and IFN-K. It is thus an autoimmune condition where the body's immune system attacks its joints. In gouty arthritis, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Osteoarthritis is a degenerative cartilage disorder; cartilage breakdown causes bones to rub against each other. Causes include injuries, diseases such as Paget's disease, and long term obesity, but often the cause is unknown, and the full mechanism has not been discovered. It is treated with NSAIDs and COX-2 inhibitors. Complicating matters further is that fibromyalgia is sometimes also intended to be included in the loose term "arthritis". There is also Psoriatic Arthritis (including DIP, and spondylitis) which is believed to be autoimmune in origin but is a separate disorder from RA. There are also an assortment of infectious arthritis, i.e. arthritis caused by bacteria, rickettsiae, mycoplasmas, viruses (or vaccinations given to prevent viral infections), fungi, or parasites. Included in this category are various types of septic arthritis and mycotic arthritis, and viral arthritis, such as rubella arthritis, Lyme arthritis (caused by a spirochete transmitted by a tick), Mumps arthritis, arboviral arthritis, syphilitic arthritis, parvovirus arthritis, tuberculous arthritis, Varicella arthritis, gonococcal arthritis, rubella arthritis, Reiter's syndrome (which includes a form of arthritis commonly arising from infection by Chlamydia trachomatis) etc. These assorted disorders can arise from quite varied sources. Thus, in addition to the above, CPDD,

sometimes called pseudoosteoarthritis, or pseudogout, arises from Calcium Pyrophosphate Deposition. It is treated with nonsteroidal anti-inflammatory drugs , corticosteroids and Colchicine. Menopausal arthritis is due to ovarian hormonal deficiency. Neuropathic arthritis (which comes in several forms, such as Charcot's disease) can arise from sources as diverse as Diabetes Mellitus, Steroid treatment, Leprosy, Chronic alcoholism, Heavy metal poisoning and Neoplastic peripheral neuropathy. Arthritis can also arise from injury to the supporting ligaments or other structures contained within or associated with the joint, a condition often called post-traumatic arthritis. Juvenile Dermatomyositis (JDMS) is an inflammatory disease of unknown cause that affects the skin, muscle and the gastrointestinal tract. Polymyalgia Rheumatica (PMR) causes severe stiffness, aching and pain in the neck, shoulders, upper arms, lower back, hips or thighs. Polymyositis is due to inflammation of skeletal muscle, resulting in weakness.

Sinusitis is the inflammation of the mucosal lining of one or more of the 4 cavities near the nasal passages (ethmoid, maxillary, frontal, and sphenoid sinuses). It commonly accompanies upper respiratory viral infections which obstruct the opening, but such obstruction can also arise from abnormalities in the structure of the nose, enlarged adenoids, diving/swimming, infections from a tooth, trauma to the nose, and foreign objects that are stuck in the nose. Bacteria, notably Streptococcus pneumonia, Haemophilus influenza, and Moraxella catarrhalis grown in the trapped secretions. In most cases it requires no treatment, but antibiotics may be given, along with acetaminophen for pain and nosedrops, for relief of symptoms.

Pharyngitis is infection and inflammation of the throat (including the nasopharynx, uvula, and soft palate)and tonsillitis is of the tonsils. These are caused by a variety of

viruses (adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, Herpes simplex virus), mycoplasmas (e.g. Mycoplasma pneumoniae), and bacteria (Group A Beta Hemolytic Streptococci (GABHS), Streptococcus pyogenes, Neisseria Gonorrhea, Hemophilus Influenza Type B) as well as fungal infections, parasitic infections, cigarette smoke, and unknown causes.

Similarly, Osteomyelitis is the inflammation of bones, often caused by bacteria (most commonly Staphylococcus Aureus), and sometimes by fungi or viruses. Chronic Recurrent Multifocal Osteomyelitis (CRMO), a chronic inflammatory disease of unknown etiology, results in recurrent fever and the development of multiple inflammatory bone lesions.

Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza.

Pneumonia is an inflammation of the lungs. Lobar pneumonia affects one or more sections (lobes) of the lungs. Bronchial pneumonia (or bronchopneumonia) affects patches throughout both lungs. Bacterial pneumonia is caused by various bacteria notably Streptococcus pneumoniae. Viral pneumonia is caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), Other causes are fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents. Treatment may include antibiotics for bacterial pneumonia. Antibiotics may also speed recovery from mycoplasma pneumonia and some special cases. There is no clearly effective treatment for viral pneumonia.

Adult (or Acute) Respiratory Distress Syndrome (ARDS) is severe inflammation in both lungs resulting in an inability of the lungs to function properly. ARDS is a

devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. No specific therapies currently exist for ARDS patients. Treatment primarily involves supportive care in an intensive care unit , including use of a mechanical ventilator and supplemental oxygen to help patients breathe.

Chronic bronchitis is a long-term inflammation of the bronchi, which results in increased production of mucus, as well as other changes. Chronic bronchitis has no specific organism recognized as the cause of the disease. Cigarette smoking is cited as the most common contributor to chronic bronchitis, followed by bacterial or viral infections and environmental pollution. Treatment is purely supportive and may include bronchodilators for inhaled medications, oxygen supplementation, lung reduction surgery and lung transplantation.

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air passageways, which can become clogged with mucus

and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself.

Acute bronchitis is the inflammation of mucous membranes of the bronchial tubes and is usually caused by infectious agents such as bacteria or viruses. It may also be caused by physical or chemical agents -- dusts, allergens, strong fumes -- and those from chemical cleaning compounds, or tobacco smoke. (Acute asthmatic bronchitis may happen as the result of an asthma attack, or it may be the cause of an asthma attack.) Acute bronchitis is usually a mild, and self-limiting condition, with complete healing and return to function. Most of the treatment is supportive of the symptoms, and may include analgesics, such as acetaminophen for fever and discomfort.

Asthma is a chronic, inflammatory lung disease involving recurrent breathing problems. It is characterized by three airway problems: obstruction, inflammation, and hyper-responsiveness. These lead to contraction of airway muscles, mucus production, and swelling in the airways. There are many different asthma triggers.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Mucocutaneous lymph node syndrome (MLNS) or Kawasaki syndrome is a potentially fatal inflammatory disease that affects the heart, circulatory system, mucous membranes, skin, and immune system. Its cause is unknown.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is the inflammation of the meninges—the surrounding 3-layered membranes of the brain and spinal cord, and the fluid it is bathed in, (CSF). It can be caused by virtually any known infectious agent. Thus, if it is caused by Haemophilus influenzae or Neisseria meningitis, the antibiotic derivative rifampin would be used.

Myelitis is inflammation of the spinal cord.

Dactylitis is an inflammatory affection of the fingers.

Inclusion body myositis in an inflammatory slowly progressive proximal myopathy which may cause dysphagia and mild to moderate muscle wasting. Steroids and immunosuppression have generally been generally ineffective. Its pathogenesis is unknown, but ubiquitin, prion protein, and tau protein has been found in these inclusions.

Behçet's disease is a syndrome of unknown origin, but appears to be an autoimmune disorder. It is characterized primarily by inflammation of the blood vessels. Symptoms include a broad range of problems, which include mouth sores, genital sores, skin sores or lesions, meningoencephalitis, Uveitis, inflammation of the joints, thrombophlebitis, aneurysms, digestive tract ulceration (sometimes called Behçet's colitis)

Encephalitis is inflammation of the brain itself, often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Inflammation in the brain is a significant component of some important neurodegenerative conditions, including Alzheimer's Disease, AIDS dementia, Pick's Disease, Parkinson's Disease, and Huntington's Disease. The circumstances here are poorly understood because while there does not appear to be lympho-infiltrative processes, there is neuropathological evidence for immune activation. Thus, inflammation may be a disease-aggravating or even a disease-ameliorating factor in pathogenesis, or a non-contributory consequence of the injurious cascade of neurodegeneration and thus incidental.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also take the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids is an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything which obstructs the free

circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanliness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the body's exterior. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when Neisseria gonorrhoeae is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially Candida albicans), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis),

treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Another category of inflammatory disorders is Interstitial lung disease, or ILD, (interstitial pulmonary fibrosis), a term that includes more than 180 chronic lung disorders, which may be chronic, nonmalignant (non-cancerous) and noninfectious. Interstitial lung diseases are named after the tissue between the air sacs of the lungs called the interstitium -- the tissue affected by fibrosis (scarring). The common link between the many forms of ILD is that they all begin with an inflammation. The three main kinds are bronchiolitis - inflammation that involves the bronchioles (small airways); alveolitis - inflammation that involves the alveoli (air sacs); and vasculitis - inflammation that involves the small blood vessels (capillaries). More than 80 percent of interstitial lung diseases are diagnosed as pneumoconiosis, a drug-induced disease, or hypersensitivity pneumonitis. An important group of the ILDs are the Idiopathic interstitial pneumonias including idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia, Respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia and lymphoid interstitial pneumonia. Other ILDs are bronchiolitis obliterans, histiocytosis X, chronic eosinophilic

pneumonia, granulomatous vasculitis, Goodpasture's syndrome and pulmonary alveolar proteinosis. The cause of interstitial lung disease is not known, however, a major contributing factor is thought to be inhaling environmental pollutants. Other contributing factors include Sarcoidosis, certain drugs, radiation, connective tissue or collagen diseases and family history. Treatments may include corticosteroids, influenza or pneumococcal pneumonia vaccine but these are of limited effectiveness.

Many Occupational Lung Diseases are inflammatory in origin, arising from repeated and long-term exposure to certain irritants on the job. These include for example asbestosis, coal worker's pneumoconiosis (caused by inhaling coal dust), silicosis (caused by inhaling free crystalline silica), byssinosis (caused by dust from hemp, flax, and cotton processing, also known as brown lung disease), aluminosis, anthracosis ("collier's lung", from the accumulation of carbon from inhaled smoke or coal dust in the lungs), chalicosis (stone-cutters' lung disease, due to inhaling stone dust), siderosis (occurring in iron workers, produced by the inhalation of particles of iron), tabacosis, hypersensitivity pneumonitis (caused by the inhalation of fungus spores from moldy hay, bird droppings, and other organic dusts and occupational asthma (caused by inhaling certain irritants in the workplace, such as dusts, gases, fumes, and vapors).

Proctitis is a form of inflammation of the rectum, and includes Antibiotic-Induced Proctitis, Gonorrheal Proctitis, Herpetic Proctitis, Ischemic Proctitis, Radiation Proctitis, Syphilitic Proctitis and idiopathic proctitis.

Pulmonary Sarcoidosis causes small lumps, or granulomas, which generally heal and disappear on their own. However, for those granulomas that do not heal, the tissue can remain inflamed and become scarred, or fibrotic. Pulmonary sarcoidosis can develop

into pulmonary fibrosis. Bronchiectasis, a lung disease in which pockets form in the air tubes of the lung and become sites for infection, can also occur. Treatment may include the use of corticosteroids.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as Candida albicans, dentures, chemotherapy and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to Lactobacillus capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Rhinitis is a reaction that occurs in the eyes, nose and throat when airborne irritants (allergens) trigger the release of histamine. Histamine causes inflammation and fluid production in the fragile linings of nasal passages, sinuses, and eyelids. The two categories of rhinitis are allergic rhinitis (seasonal and perennial) and nonallergic Rhinitis (including eosinophilic, rhinitis medicamentosa, vasomotor Rhinitis, neutrophilic rhinosinusitis, and others), which come from fumes, odors, temperature or atmospheric changes, smoke, etc. Treatments for nonallergic rhinitis include oral medications, inhaled medications, immunotherapy, and surgery for some conditions. Wegener's Granulomatosis is a disease that usually begins as a localized granulomatous inflammation of upper or lower respiratory tract mucosa and may progress into generalized necrotizing granulomatous vasculitis and glomerulonephritis. The cause is unknown. Although the

disease resembles an infectious process, no causative agent has been isolated. Treatment is with immunosuppressive cytotoxic drugs.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is a type of inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine. Vogt-Koyanagi-Harada syndrome (Harada's disease) is an acute inflammatory, immune-mediated disorder that can cause choroidal neovascularization, severe chorioretinal atrophy, and secondary glaucoma.

River blindness arises from inflammation of the eye caused by larvae (microfilaria) of the nematode ***Onchocerca volvulus***, although the ***Wolbachia*** bacteria may be involved as well.

Multifocal choroiditis and panuveitis (MCP) is a posterior chorioretinal inflammatory disease of unknown etiology

There ar also other forms of choroiditis, inflammation of the middle coat (choroid) of the eyeball, as well as uveitis, which is inflammation of the parts of the eyes that make up the iris. Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from Helicobacter pylori. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee string), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrowing hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. Acne's inflammation is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus Propionibacterium acnes, which populates the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in

the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), which are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

There are a number of different forms of vasculitis, including Churg-Strauss vasculitis, consecutive vasculitis, granulomatous vasculitis of central nervous system, hypersensitivity vasculitis, (called also allergic or leukocytoclastic vasculitis or leukocytoclastic angiitis which arises from hypersensitivity to an antigenic stimulus), hypocomplementemic vasculitis, isolated vasculitis of central nervous system, nodular

vasculitis, overlap vasculitis (polyangiitis overlap syndrome), pulmonary vasculitis including Wegener's granulomatosis, rheumatoid vasculitis, segmented hyalinizing vasculitis (livedo vasculitis), Polyarteritis nodosa, and urticarial vasculitis. There are also specific forms of arteritis, including coronary arteritis, equine viral arteritis, giant cell arteritis (cranial, granulomatous, or temporal arteritis or Horton's disease), infantile arteritis, infectious arteritis, arteritis obli¢terans (endarteritis obliterans), rheumatic arteritis, syphilitic arteritis, Takayasu's arteritis (aortic arch, or brachiocephalic arteritis or Martorell's syndrome or pulseless disease; it is of unknown origin), tuberculous arteritis, endarteritis obliterans, and verminous mesenteric arteritis.

Cystic fibrosis (CF) is an inherited disease characterized by an abnormality in the glands that produce sweat and mucus. It is chronic, progressive, and is usually fatal. The basis for the problem with CF lies in an abnormal gene, which results in an atypical electrolyte transport system within the cells of the body. The abnormal transport system causes the cells in the respiratory system, especially the lungs, to absorb too much sodium and water. This causes the normal thin secretions in our lungs to become very thick and hard to remove. The high risk of infection in the respiratory system leads to damage in the lungs, lung that do not work properly, and eventually death of the cells in the lungs. The most common causes for infection in the lungs are Staphylococcus aureus, Haemophilus influenza and Pseudomonas aeruginosa (PA). The disorder itself is largely untreatable.

Osgood-Schlatter disease is a common form of inflammation of the knee in active adolescents. It has no pharmaceutical treatment per se. Other inflammations of the knee include Sinding-Larsen-Johansson disease, Patellofemoral syndrome, and osteochondritis dissecans.

Adhesive capsulitis is a type of inflammation of the shoulder. Its origin is usually unknown.

There can be a generalized inflammatory response of the entire body. When it arises from a proven source of infection, it is called sepsis. When it does not, it is called systemic inflammatory response syndrome (SIRS). Both of these are characterized by extensive cytokine dysregulation.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It should be noted that determining that a disorder is an inflammatory one is sometimes not an easy manner. For example, it has taken decades of research to discover that the destruction of the central area of the retina, which is the hallmark of age-related macular degeneration, actually arises out of an inflammatory process, involving the Complement Pathway. This only became well established in 2005. It is entirely possible that a majority of disorders presented considered idiopathic --- including many untreatable disorders --- are in fact inflammatory disorders.

It must be noted that an inflammatory response is a normal body process and for good reason. A certain level of inflammatory response is needed to protect the body from invading organisms, especially bacteria, viruses, and parasites. An acute inflammatory response is needed to activate the healing process for burns, mediated by a range of MMPs. In sprains or other ligament injuries, some inflammatory response is needed initially to initiate repair of the damage. In mechanical wounds, some inflammatory response is required for satisfactory wound healing and indeed anti-inflammatory drugs such as cortisone can impair healing when administered at the time of wounding. In fact,

inflammation is too important to be dependent on a single pathway and so inflammation can be initiated by numerous different systems, and generally, if one fails or is thwarted, another can do some or all of the job.

II. The actual scope of "autoimmune diseases" is not entirely clear, since for many disorders (Autism, Primary sclerosing cholangitis (PSC), Multiple Sclerosis, Idiopathic pulmonary fibrosis, Phacogenic Uveitis, adhesive capsulitis, fibromyalgia, Bullous pemphigoid, Polymyositis, Rosacea, Hidradenitis suppurativa, Multifocal Motor Neuropathy with conduction block (MMN), Polymyalgia Rheumatica, and Still's disease), there remains considerable dispute over whether it is or is not best understood as an autoimmune disorder. The "autoimmune diseases" are processes that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes. Known autoimmune disorders, or disorders generally considered to be autoimmune include Polymyositis, Scleroderma, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), Meniere's disease, Omenn syndrome, Idiopathic neutropenia, Idiopathic thrombocytopenic purpura, Autoimmune hemolytic anemia, Premature ovarian failure, Idiopathic hypoparathyroidism, primary biliary cirrhosis, Pemphigus, multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, Silent thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute

necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss (IPBSNHL), aplastic anemia, pure red cell anemia, polychondritis, Stevens-Johnson syndrome, Alopecia areata, asthma, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, Reiter's syndrome, Sjogren's Syndrome, Goodpasture Syndrome, inflammatory bowel disease, Essential Mixed Cryoglobulinemia, Behçet's Syndrome, Chronic Inflammatory Polyneuritis (CIPD), CREST Syndrome, Antiphospholipid Syndrome, Relapsing Polychondritis (systemic chondromalacia or von Meyenburg disease), Retroperitoneal Fibrosis, Celiac disease, Vitiligo, "immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome" (IPEX), Autoimmune Atherosclerosis and many more.

III. AIDS. AIDS is listed, but note that this directly contradicts the previous group. That is autoimmune disorders arise from an overactive immune system, whereas AIDS arises from a pathologically inactive immune system.

IV. Drug dependence and substance abuse. Drug dependence is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Dependence on barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette depedence arises from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc.

V. Fibrosis. Fibrosis is the formation or development of excess fibrous connective tissue in an organ or tissue. Fibrosis would thus cover Endomyocardial Fibrosis, Oral Submucous Fibrosis Dermatology, Pulmonary Fibrosis (including bibasilar pulmonary fibrosis, Idiopathic Pulmonary Fibrosis, Interstitial Pulmonary Fibrosis, Interstitial Lung Disease) Coal Worker's Pneumoconiosis Medicine, Congenital Hepatic Fibrosis, osteodystrophia fibrosa, osteitis fibrosa disseminata, Ledderhose disease (LD), Cystic Fibrosis, Deltoid Fibrosis, Localized Fibrosing Disorders(including morphea, generalized morphea, linear scleroderma, retroperitoneal fibrosis, mediastinal fibrosis, and Dupuytren contracture), Cirrhosis, Cystic Fibrosis, reactive fibrous hyperplasia , Osteofibrous dysplasia, Fibrous dysplasias (which occur in several forms), Eosinophilic Fasciitis, nodular subepidermal fibrosis, and Fibrolamellar Carcinoma. It would include all types of fibromas including Infantile myofibromatosis, Fibrous hamartoma of infancy. Juvenile hyaline fibromatoses. Infantile digital fibromatoses. Calcifying aponeurotic fibromas. Giant cell fibroblastoma. Ovarian fibroma, Dermatofibroma, myofibroma, myofibromatosis, desmoplastic fibroma, neurofibroma, peripheral odontogenic fibroma, peripheral ossifying fibroma, giant cell fibroma, Chondromyxoid Fibroma, Oral Neurofibroma, Juvenile aponeurotic fibroma (JAF), aggressive infantile fibromatosis (AIF), omental fibroma, Perifollicular fibroma, ameloblastic fibroma, Premalignant Fibroepithelial Tumor (Pinkus Tumor), Periungual fibroma (Koenen tumor), desmoid tumor, tracheal fibroma and many others. It also includes Myelofibrosis , tubulointerstitial fibrosis, cerebriform mesodermal hamartomatous and Proteus syndrome, Atelectasis, fibrous cortical defect (FCD), Acquired Digital Fibrokeratoma, fibrofolliculomas, tubulointerstitial fibrosis, Endometriosis, Progressive massive fibrosis (a complication of coal workers' pneumoconiosis), Nephrogenic systemic

fibrosis Injection fibrosis (which can occur as a complication of intramuscular injections), Erythromelalgia, Meckel-Gruber Syndrome, Milroy Disease, Superficial fibromatosis (SF), postradiation fibrosis, Infantile digital fibromatosis (IDF), polyfibromatous syndrome, Riedel thyroiditis, Juvenile Nasopharyngeal Angiofibroma (JNA), uterine fibroids, localized fibrous tumor of the pleura (LFTP), Systemic Sclerosis, Peripelvic fibrosis, fibrosarcomas (including congenital fibrosarcoma, adult-type fibrosarcoma, sclerosing epithelioid fibrosarcoma and myxofibrosarcoma) and many, many other disorders. Fibers occur all over the body, and numerous things can go wrong with their growth and development.

VI. The claim also covers such diverse items as Alsz, CHF, hypertension, renal failure (which can arise from many, many different causes), biliary colic, sclerosis, etc.
(2) The nature of the invention and predictability in the art: The invention is directed toward the treatment of disease and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See ***In re Fisher***, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).
(3) Direction or Guidance: That provided is very limited. The dosage information appears to have been omitted from the specification.
(4) State of the Prior Art: These compounds are 7-aminoalkyl Xanthines with a particular substitution pattern in the 3-position and 8-position. So far as the examiner is aware, no 7-aminoalkyl Xanthines of any kind have been used for the treatment of any of these disorders.

(5) Working Examples: There are none to the treatment of any disease. Indeed, no biological date of any kind appears.

(6) Skill of those in the art:

I. Inflammation. One of ordinary skill in the art knows that there is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, histamine, fibrin, some PDE4 isoenzymes, kallikrein, plasmin, thrombin, PAF, Mac-1, VLA-4, VLA-5, VLA-6, VCAM-1, LFA-1, ICAM-1, Prostaglandins and cyclic endoperoxides (particularly prostacycline, prostaglandin E2, and thromboxane A2), leukotrienes (especially LTB4, LTC4, LTD4, and LTE4) and cytokines, and many, others. Examples of pro-inflammatory cytokines include IL-1-alpha, IL-1beta, IL-6, IL-8, IL-11, IL-12, IL-17, IL-18, GM-CSF, CNTF, OSM (Oncostatin M), MCP-1, CCL5 (RANTES), TGF-beta, ENA-78, Osteopontin, Cyclophilin A, LIF (leukemia inhibitory factor), leptin, MIP-1, TWEAK, MGSA, keratinocyte-derived chemokine, PF4, MCP-1 (GDCF), IFN-gamma, TNF-α, Abscisic acid, high mobility group box chromosomal protein 1 (HMGB-1), S100A12 (EN-RAGE), TRAIL, sCD40L, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-32, and IL-33. The Complement Pathway, which exists in two separate branches, uses C1, C4a, C4b, C2, C3a, C3b, C5a, C5b, C6, C7, C8 and C9, as well as the membrane attack complex (MAC) and other complexes, C3 and C5 convertase enzymes, PI3K-gamma, Magnesium ions, and Factors B, D, F, H, etc.

One of ordinary skill in the art also knows that mediation of inflammation is among the most pervasive and complex of all body process. There are very complex interactions among just the cytokines. As a second example, the Hageman factor is a protein that initiates three different processes: a) the intrinsic clotting process which operates via

thrombin and fibrin, b) the fibrinolytic system which produces fibrinolysis via plasmin and 3) the kallikrein/kinin cascade, which produces the kinins, e.g. bradykinin. Further, Plasmin can also activate C3 and C5 in the complement cascade (an entirely separate set of vascular events) producing C3a and C5a, respectively, as can thrombin.

One of ordinary skill in the art also knows that there are many paradoxical features in the inflammation system. As an example, in lung inflammation, nitric oxide appears to be a pro-inflammatory mediator in acute situations e.g. ARDS but anti-inflammatory in more stable situations. As a second example, the cytokine TGF-beta-1 possesses both pro-inflammatory and anti-inflammatory activities. Virtually all cells have TGF-beta-1 receptors, and the cytokine has many other roles other than in inflammation. As a third example, CRF appears to have both pro-inflammatory and anti-inflammatory activities.

And in fact, there is a tremendous diversity in the combination of mechanisms that produce inflammation For example, Atherosclerosis arises from the accumulation of macrophage white blood cells and is promoted by low density (especially small particle) lipoproteins. Very few, if any, other inflammatory disorders have this particular mechanism.

Thus, one of ordinary skill in the art knows that, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

For a compound or genus to be effective against inflammation generally is contrary to the present understanding of medical science. Thus, it is not reasonable for any agent to be able to treat inflammation generally. That is, the skill is so low that no compound effective generally against inflammatory disorders has ever been found. In terms of the individual

inflammatory disorders, this is completely varied. It ranges from areas where the skill level is high, as in asthma, to ARDS, where the skill level is so low that there is no effective pharmacological treatment.

II. Autoimmune. This very much depends on the particular art area.
I. There are both chronic and acute "autoimmune diseases", most of which lack satisfactory treatment. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. In fact, there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own

immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis. 3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. Autoimmune disorders can arise from the killer T-cells, from the helper T-cells, or from the regulatory T-cells (e.g. IPEX syndrome). 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE. Thus, with such differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found.

II. Autoimmune disorders are among the most complex and difficult to understand of all major categories of human disease. An example of this is scleroderma, which kills thousands of Americans every year. It is not even clear if the disorder is best understood as a vascular disease, a fibrotic disease, or an immune disease. Its cause—or causes—remains murky. Its molecular mechanisms or genetic origins have never been nailed down. Partially as a result, no compound has ever been established as effective in treating the disorder itself. While anti- TGF- β drugs have been given to reduce fibrotic scars, and ACE inhibitors provided to protect the kidneys, and still others are given to combat pulmonary hypertension, none of these combat scleroderma itself. While some general immunosuppressive drugs

showed promising results even in Phase II studies, as of the filing date, and even now, none have ever been established as effective against scleroderma.

III. IBD is a generic term for an entire family of disorders, the most important of which are Ulcerative colitis and Crohn's disease. Less common forms include lymphocytic colitis, collagenous colitis, Ischaemic Colitis, Behçet's Syndrome, and Infective Colitis. IBD arises from a ranges of causes, known and unknown. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, for example are idiopathic.

IV. Autoimmune neuritis is any inflammation of the nerves arising from the body's own immune system, and includes Guillain-Barre Syndrome and Miller Fisher Syndrome. GBS is often preceded by a viral or bacterial infection, surgery, immunization, lymphoma, or exposure to toxins. Demyelination occurs in peripheral nerves and nerve roots, and weakness of respiratory muscles and autonomic dysfunction may occur. Miller Fisher Syndrome involves oculomotor dysfunction, ataxia, and loss of deep tendon. The ataxia is

produced by peripheral sensory nerve dysfunction. Facial weakness and sensory loss may also occur. The process is mediated by autoantibodies directed against a component of myelin found in peripheral nerves. GBS and Miller Fisher Syndrome are both quite refractory. Conventional immune suppressant drugs such as methylprednisolone have not been effective, and so the skill level in these disorders is low. Only plasma exchange therapy and intravenous immune serum globulin (IVIG) have proven effective.

Examples of pharmaceutically untreatable autoimmune disorders include celiac disease, APECED, scleroderma and ALS. Medicines can be given to relieve symptoms, e.g. replace missing hormones, combat pulmonary hypertension or ameliorate pain, but these pharmaceuticals do not treat the disease itself.

III. AIDS. The only AIDS treatment that have ever succeeded are those that inhibit HIV enzymes. That is not a property that these compounds are described as having. Thus, the skill level in the art of treating AIDS by compounds which do not do enzyme inhibition is essentially nil.

IV. Drug dependence and abuse. All attempts to find a pharmaceutical to treat chemical depedence generally have thus far failed. The notion that a compound could be effective against chemical dependencies in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for addiction generally. That is because, as noted above, different drugs operate on different parts of the brain. In general, treating the chemical dependency is done through various forms of therapy. Pharmacological approaches generally involve antagonizing this or that receptor, and obviously, no compound can block receptors generally. If it did, such a compound would probably be lethal to the body.

V. Fibrosis. A general treatment of fibrosis cannot be reasonably be expected to be found, in large part because fibrotic process tend to be somewhat different in different organs. For example, Sickle-cell anemia can cause fibrosis of the spleen, and Cystic fibrosis can trigger fibrosis of the pancreas, but these are fairly different processes. Even in the same origin, there are important differences in the fibrotic process between Idiopathic pulmonary fibrosis of the lung, lung fibrosis arising from TB, and lung fibrosis arising from cystic fibrosis.

VI. Alzheimer's Disease. The skill level for Alzheimer's Disease is considered low. Alzheimer's Disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research, exceeded in recent years only by research into AIDS and cancer. The channel hypothesis of Alzheimer's disease proposes that the beta-amyloid peptides which accumulate in plaques in the brain actually damage and/or kill neurons by forming ion channels. An abnormal phosphorylation of tau proteins is being investigated as one of the important events in the process leading to their aggregation. There appears to be a specific alteration of a p53-mediated intracellular pathway involved in sensing and repairing DNA damage in peripheral cells, and the role of neuronal apoptosis is under investigation. But even as of 2007, there are great unknowns relating to the links between amyloid-ß and tau, to the mechanisms that determine the selective vulnerability of defined neuronal and glial populations, and to the molecular species that cause nerve cell degeneration. Many kinds of therapies have been investigated in the past, including Hydergine-LC (actually approved by the FDA for Alzheimer's Disease, but later determined to make the disease worse), Cu/Zn chelators (or Cu and Zn homeostasis regulators), endothelin B receptor agonists, α-TNF inhibitors, angiotensin II receptor antagonists, ACE

inhibitors, EAA agonists (including partial agoinists), estrogens, metabotropic receptor agonists, muscarinic M2 receptor antagonists, free-radical scavengers, butyrylcholinesterase inhibitors, cholinergic agonists, potassium-channel blockers, P38 kinase inhibitors, sigma-1 Receptor Agonists, 5-HT1A receptor antagonists, α secretase stimulants, and others. From this immense body of work, only two kinds of drugs ever emerged. Four Acetylcholinesterase inhibitors were found to have some limited value: tacrine (Cognex®, no longer clinically used); donepezil (Aricept®); galantamine (Razadyne®/Reminyl®/Nivalin®) and rivastigmine (Exelon®). In addition, one voltage-dependent NMDA-antagonist, Memantine (Axura®/Akatinol®/Namenda®/Ebixa®) was also found effective. Categories of agents and techniques under investigation as of 2007 include Aß aggregation inhibitors, assorted antioxidants, γ-Secretase modulators, γ-Secretase inhibitors, NGF mimics, PPAR agonists, HMG-CoA reductase inhibitors (statins), Ampakines, Calcium channel blockers, GABA receptor antagonists, Glycogen synthase kinase inhibitors, Intravenous immunoglobulin, Muscarinic receptor agonists, cholinesterase inhibitors, Nicotinic receptor modulators, Passive Aß immunization, Phosphodiesterase inhibitors, Serotonin receptor antagonists, Active Aß immunization, NGF gene therapy, H_3-receptor antagonists, NSAIDs (including NO-NSAIDs and COX-2 Inhibitors), and CB_1 and CB_2 cannabinoid receptor agonists. It is or course entirely possible that one or more of these will eventually be made to work. However, as can be seen by the many, many categories of drugs which never panned out, so simply being the subject of active investigation is no indication that enablement is present at that time. The skill level in this art is so low that only Acetylcholinesterase inhibitors and NMDA-antagonists have been made to work.

VII. Treatment for diabetes insipidus depends on what is causing the disease. Causes range from a hypothalamus that produces too little ADH, a malfunctioning pituitary gland that fails to release ADH into the bloodstream, assorted brain injuries, encephalitis, meningitis or blockage in the arteries leading to the brain, certain tumors, tuberculosis and sarcoidosis, as well as some hereditary causes as well. Type II Diabetes is a metabolic disorder.

VIII. Parkinson's Disease. The skill level is very low relative to the difficulty of task. Parkinson's Disease is a neurodegenerative disorder which, like most neurodegenerative disorders, has been highly resistant to pharmaceutical treatment. The disease is characterized by the degeneration and death of dopamine-producing cells in the substantia nigra, located in the midbrain, along with the presence of cytoplasmic protein inclusions called Lewy bodies. PD is considered to be a cluster of related disorders. The majority of cases of PD are deemed sporadic, but there are also familial forms of PD. This death is of unknown origin (idiopathic), and cannot itself be stopped. Current drug regimens for Parkinson's disease are aimed instead at symptomatic relief, primarily through a dopaminergic effect. This includes dopamine replacement therapy (L-dopa), COMT inhibitors (which facilitate the conversion of L-Dopa to dopamine itself), Amantadine (which appears to increase dopamine synthesis in the remaining cells), dopamine agonists (which mimic dopamine) or MAO B inhibitors (e.g. Selegeline which reduces or delays the breakdown of dopamine). These do not actually treat the disease itself, but instead seek to boost the amount of dopamine available by various mechanisms. At the time of filing, and indeed at present, no drug has been scientifically demonstrated to treat the disease itself,

rather than provide relief for this or that symptom, such as bradykinesia, tremors, and other motor symptoms, constipation, poor balance, etc.

(7) The quantity of experimentation needed: Owing to the factors listed above, especially in points 1(b), 4 and (6), experimentation needed will be extensive. Because of the sheer scope of this claim language, dozens of unrelated diseases will have to be tested. Many of these are already known to be resistant to pharmacological treatment as noted above.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. ***In re Wright***, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Objections

Claims 7-21 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. For claims 7-1, to the extent that these have an additional group, or an additional group plus a spacer, these are not provided for in the first place by claim 1, which makes no provision for such additional

groups such as biotin to be attached. A similar problem exists for claims 17-21 with regard to some (unspecified) "atoms bonded thereto". These are not provided for in claim 1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Mark L. Berch/ whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/
Primary Examiner
Art Unit 1624

4/24/2009